

Remarks

I. Status of the Claims

Reconsideration of this application is respectfully requested.

By the foregoing amendments, claims 74-76 are cancelled without prejudice to or disclaimer of the subject matter therein. These amendments are sought to place the claims into condition for allowance or for consideration on appeal, and introduce no new matter. Entry and consideration of these amendments are respectfully requested.

Upon entry of the foregoing amendments, claims 50-59 are pending in the application, with claim 50 being the independent claim.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

II. Summary of the Office Action

In the Office Action dated July 20, 2005, the Examiner has made or maintained four rejections of the claims. Applicants respectfully offer the following remarks concerning each of these elements of the Office Action.

III. The Rejection Under 35 U.S.C. § 112, First Paragraph Is Traversed

In section 7 of the Office Action at pages 2-3, the Examiner has rejected claims 50-59 and 74-76 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. As indicated above, claims 74-76 have been cancelled without prejudice or disclaimer, thus rendering moot the portion of the

rejection that applied to these claims. Applicants respectfully traverse this rejection as it may be applied to the remaining claims.

In making the rejection, the Examiner alleges that "[c]laim 50, recite[s] new matter as follows: 'and less than about 10% of said uricase is in a non-tetrameric aggregated form.'" *See* Office Action at page 3. The Examiner contends that the "specification . . . does not contain the recited language claimed. . . . Furthermore, no were [sic] in the specification can the combination of 'at least about 90%' and 'at less than about 10% . . .', as recited in claim 50, can be found." *See* Office Action at page 3.

Applicants wish to remind the Examiner that "[a]dequate description under the first paragraph of 35 U.S.C. 112 does not require *literal* support for the claimed invention the observation of a lack of literal support does not, in and of itself, establish a *prima facie* case for lack of adequate descriptive support under the first paragraph of 35 U.S.C. 112." *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. Int. 1994). Instead, the written description requirement of 35 U.S.C. § 112, first paragraph, is met "if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an [applicant] had possession of the concept of what is claimed," *id.*, *i.e.*, "[I]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification" *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

In the present case, the specification provides numerous examples of support for the recited claim language. First, as indicated in the Reply Under 37 C.F.R. § 1.111 filed May 26, 2005, the specification discloses that by using the present invention, "at least

90% [of the uricase] may be in the tetrameric form; the undesirable aggregates may thus constitute as little as about 10% . . . , or less, of the total isolated uricase." *See* specification at page 17, lines 3-5. Furthermore, the specification discloses that "the purified tetrameric uricase may contain less than about 10% uricase aggregates." *See* specification at page 10, lines 27-29. Finally, claim 40, as originally filed, provides support for the present claim language by reciting "less than about 10% uricase aggregates." *See* specification at page 32, lines 29-30. Given that the invention as presently claimed is directed to the isolation of tetrameric uricase in which "at least about 90% is in a tetrameric form," by *definition* the claimed uricase preparations *must* contain less than about 10% non-tetrameric aggregates (since if the preparations had *more* than 10%, the total would exceed 100% which is impossible). Thus, one of ordinary skill in the art would understand that "less than about 10% *uricase aggregates*," as recited in the specification, is the same as "less than about 10% *non-tetrameric aggregates*" as recited in the present claims. Therefore, one of ordinary skill in the art would readily appreciate that Applicants possessed what they claim as of the filing date of the application.

Moreover, the Examiner's statement in the second full paragraph on page 3 of the Office Action -- that "no were [sic] in the specification can the combination of 'at least about 90%' and 'at less than about 10% [sic] . . . ', as recited in claim 50, can be found" -- is irrelevant. As noted above, U.S. patent law does not require *in ipsi verbis* support for recitations in a claim. *See Parks* and *Alton*. In the present case, as also noted above, one of ordinary skill would have readily understood that if a given preparation of isolated uricase contained "at least about 90%" of the uricase in a tetrameric form, then the amount of uricase in a non-tetrameric aggregated form *must* be "less than about 10%,"

since the total amount of uricase in the preparation cannot exceed 100%. Therefore, the Examiner's contention that these recitations of claim 50 are not explicitly stated together, even if true, is irrelevant to the question of patentability of the present claims, since one of ordinary skill would have understood that the recitation of "less than about 10%" non-tetrameric aggregated uricase simply makes explicit in the claims that which was previously at least implicit. Hence, this contention cannot be used as a basis for a rejection under 35 U.S.C § 112, first paragraph.

Thus, under *Parks* and *Alton*, the present specification clearly provides sufficient written description to convey to one of ordinary skill that Applicants had possession of the full scope of the claimed invention upon filing of the application. In view of the foregoing remarks, Applicants respectfully assert that claims 50-59 are fully described in the specification as filed. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are therefore respectfully requested.

IV. The Rejection Under 35 U.S.C. § 102(b) Is Traversed

In section 8 of the Office Action at pages 3-7, the Examiner has rejected claims 50-53 under 35 U.S.C. § 102(b) as anticipated by Lee *et al.*, *Science* 239: 1288-1291 (1988) (hereinafter "Lee"). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that Lee discloses the purification of porcine and murine tetrameric uricases that contain at least about 90% tetrameric uricase because the reference mentions that porcine and murine urate oxidase were "purified to homogeneity." See Lee at page 1289. The Examiner thus interprets a "homogeneous" preparation of uricase in Lee to encompass a preparation in which at

least about 90% of the uricase is in tetrameric form. *See* Office Action at pages 4-5. Furthermore, the Examiner points to a statement in Lee that mammalian uricase "is associated with the peroxisome and exists as a tetramer with an apparent subunit size of 32,000 daltons" to support his contention that the mammalian uricase disclosed in Lee was 100% in the tetrameric form. *See* Lee at page 1288. Applicants respectfully disagree with these contentions, and with this interpretation of Lee upon which these contentions are based, for at least the following reasons.

First, contrary to the Examiner's apparent contention, Lee does not *expressly* disclose preparations of isolated uricase in which at least about 90% of the uricase is in a tetrameric form, as recited by the present claims. This reference only indicates that porcine liver and murine urate oxidase were purified to homogeneity. This reference does *not* indicate that at least about 90% of the "purified" uricase was in a tetrameric form. Indeed, the reference does not indicate in *what* form the "purified" uricase was, let alone that at least about 90% of it was in a tetrameric form.

Second, while the Examiner is correct in his assertion that mammalian uricase *in vivo*, *e.g.*, when the uricase is associated with the peroxisome, exists as a tetramer, Applicants respectfully point out that *prior to* the present invention, *isolated* preparations of natural and recombinant uricase, including those disclosed in Lee, contained a *mixture* of forms of the enzyme, including high amounts of non-tetrameric aggregates. *See* specification at page 16, lines 5-16. The estimated percentage of the non-tetrameric aggregated form of the enzyme present in such *purified and isolated* preparations varies from more than 10% to about 80%. *See id.* Therefore, prior to the present invention, it was not possible to isolate tetrameric uricase, wherein at least about 90% of the uricase is

in a tetrameric form. Indeed, using the methods disclosed in Lee, uricase present in a tetrameric form in the tissue, *i.e.*, *unisolated* uricase, would not remain in a tetrameric form upon being isolated from the tissue. Instead, the Lee methods would lead to rapid aggregation of the isolated uricase resulting in preparations in which less than about 90% was in a tetrameric form (and thus, in which more than about 10% was in a non-tetrameric aggregated form).

Contrary to the Examiner's contentions, the "homogeneous" uricase preparations of Lee are *not* tetramers -- they are monomers, formed from aggregates of isolated uricase by the SDS-PAGE process used in Lee. The method employed and cited by Lee for assessing the homogeneity of the murine urate oxidase preparations disclosed in that reference *confirms* that Lee is analyzing *monomeric* subunits of uricase rather than the tetrameric form of the enzyme. See T.G. Conley and D.G. Priest, "Purification of Uricase from Mammalian Tissue," *Preparative Biochemistry* 9:197-203 (1979) (hereinafter "Conley"). Conley (and therefore Lee, *citing* Conley at page 1289, 2nd column) used SDS-PAGE to analyze the uricase. While the Examiner is correct that "in a denaturing gel such as SDS/PAGE, only the subunit form of the uricase is evident," Applicants respectfully contend that the commercial preparation of uricase obtained by Lee for use in SDS-PAGE is not in the "native tetrameric form" as asserted by the Examiner. As indicated above, prior to the present invention, uricase that is in the tetrameric form *in vivo* (*i.e.*, in an unisolated form) was known to rapidly form aggregates larger than tetramers upon being isolated from the tissue. Therefore, the authors of Lee would not be expected to have produced a uricase preparation in which at least about 90% of the uricase was in a tetrameric form; instead, more than 10% of the

uricase would have been present in a *non-tetrameric* aggregated form. Therefore, if the isolated commercial preparation of uricase used by Lee was analyzed prior to "purif[ying] to homogeneity" by SDS-PAGE, it would have been seen that that uricase preparation did *not* contain at least about 90% of the uricase in a tetrameric form and less than about 10% in a non-tetrameric aggregated form. This conclusion is further supported by the Declaration Under 37 C.F.R. § 1.132 by Merry R. Sherman, Ph.D. (hereinafter "the Sherman Declaration"), and the figures attached thereto, that was filed with Applicants' previous Amendment and Reply in the present case on May 26, 2005.

Hence, as described in the present specification, and clearly shown in the Sherman Declaration, without specifically purifying their uricase preparations to enrich for the tetrameric form over all other forms, the authors of Lee would not be expected to have produced a uricase preparation in which at least about 90% of the uricase is in a tetrameric form. Instead, the uricase preparations of Lee would be expected to contain uricase in which greater than about 10% was in a non-tetrameric aggregated form (and thus, by definition, in which less than about 90% was in a tetrameric form).

Given the discussion above, Lee therefore clearly only discloses preparations of uricase in which more than about 10% of the uricase is either: (a) in a non-tetrameric aggregated form; or (b) in a monomeric form after SDS-PAGE analysis. Lee, therefore, does *not* disclose preparations of isolated uricase in which at least about 90% is present in a tetrameric form. Indeed, Lee does not even expressly disclose purifying a tetrameric form of uricase, disclosing only the purification of uricase monomers. Thus, in disclosing "purification to homogeneity" of porcine and murine uricases, Lee is preparing uricase *monomers* and *not* uricase preparations in which at least about 90% of

the uricase is tetrameric, as is presently claimed. That is, contrary to the Examiner's contentions, "homogeneity" in Lee does *not* mean "greater than about 90% tetrameric" -- instead, "homogeneity" as used in Lee only means that the uricase has been purified away from non-uricase contaminants. This homogeneous uricase, however, could be present in *any* multimeric form or even in the monomeric form. Given that SDS-PAGE denatures multimeric proteins into their component monomeric forms, a preparation of uricase containing *any* multimeric form of the enzyme -- or even containing a *mixture* of multimeric forms -- would appear exclusively in the monomeric form after being run on an SDS-PAGE gel. Thus, this statement in Lee relating to homogeneity thus says nothing about the form, tetrameric or non-tetrameric, in which the uricase of Lee exists prior to SDS-PAGE analysis. Moreover, a homogenous preparation of isolated monomeric uricase -- which is the only isolated uricase expressly disclosed in Lee -- is not the same as an isolated tetrameric uricase which is recited by the present claims. Thus, as one of ordinary skill would readily appreciate, Lee does not disclose the production of mammalian uricases having the characteristics recited in the present claims.

While it is, of course, possible that the intermolecular association of four isolated monomers *in vitro*, under appropriate solution conditions, might theoretically make up an isolated tetrameric uricase, Lee neither expressly nor inherently discloses such preparations nor the appropriate solution conditions for producing such preparations from the monomeric subunits of uricase shown in the SDS-PAGE gels of this reference. As the Federal Circuit has held, a claim can only be anticipated by a publication if the publication describes the claimed invention with sufficient enabling detail to place the

public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). Since Lee does not disclose how one of ordinary skill might take the homogeneous isolated monomeric preparations of uricase disclosed in that reference, and produce isolated tetrameric uricase from those monomers, this reference does not enable one of ordinary skill to make the subject matter of the presently claimed invention. Accordingly, for at least these reasons, and under *Donohue* and *PPG Industries*, Lee cannot and does not anticipate the present claims.

Moreover, under 35 U.S.C. § 102, a claim can be anticipated only if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). In addition, a claim can be anticipated by a publication only if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). The Examiner has pointed to no express disclosure in Lee that would support the Examiner's statement that the "homogeneous preparations of porcine or murine tetrameric uricase comprises the at least about 90% tetrameric form of mammalian uricase claimed." Office Action at page 4. Furthermore, the present specification and

the Sherman Declaration clearly show that by preparing uricases according to the methods of Lee, one of ordinary skill at best would succeed in preparing uricases that contain *less* than about 90% tetrameric uricase. Thus, any reliance upon Lee in supporting an anticipation rejection is factually and legally unfounded.

Accordingly, Lee does not expressly or inherently disclose the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection under 35 U.S.C. § 102(b). Reconsideration and withdrawal of the rejection of claims 50-53 under 35 U.S.C. § 102(b) over Lee therefore are respectfully requested.

V. The Rejection Under 35 U.S.C. § 103(a) Is Traversed

In section 9 of the Office Action at pages 7-11, the Examiner has rejected claims 74-76 under 35 U.S.C. § 103(a) over Lee in view of Caput *et al.*, U.S. Patent No. 5,382,518 (hereinafter "Caput"). Applicants respectfully traverse this rejection. However, as indicated above, and for reasons unrelated to patentability and to this rejection, claims 74-76 have been cancelled without prejudice or disclaimer, thus rendering moot this rejection.

VI. Obviousness Type Double-Patenting Rejection

In section 10 of the Office Action at pages 12-13, the Examiner has rejected claims 50-59 and 74-76 under the judicially created doctrine of obviousness type double-patenting as being unpatentable over claims 1-30 of U.S. Patent No. 6,783,965 (hereinafter "the '965 patent"). Applicants respectfully traverse this rejection

As indicated above, for reasons unrelated to patentability or to this rejection, claims 74-76 have been cancelled without prejudice or disclaimer, thus rendering moot the portion of the rejection that applied to these claims. Applicants respectfully traverse this rejection as it may be applied to the remaining claims. However, Applicants respectfully request that this rejection be held in abeyance until subject matter that is otherwise patentable is identified, at which time Applicants will consider filing a terminal disclaimer.

VII. Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

A handwritten signature in black ink, appearing to read "Brian J. Del Buono", written over a horizontal line.

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